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Advanced Drug Delivery Reviews 56 (2004) 335–347
Advanced DRUG DELIVERY Reviews
www.elsevier.com/locate/addr

Drug polymorphism and dosage form design: a practical perspective

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Received 18 July 2003; accepted 6 October 2003

Abstract

Formulators are charged with the responsibility to formulate a product which is physically and chemically stable, manufacturable, and bioavailable. Most drugs exhibit structural polymorphism, and it is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf life under a variety of real-world storage conditions. There are occasional situations in which the development of a metastable crystalline or amorphous form is justified because a medical benefit is achieved. Such situations include those in which a faster dissolution rate or higher concentration are desired, in order to achieve rapid absorption and efficacy, or to achieve acceptable systemic exposure for a low-solubility drug. Another such situation is one in which the drug remains amorphous despite extensive efforts to crystallize it. If there is no particular medical benefit, there is less justification for accepting the risks of intentional development of a metastable crystalline or amorphous form. Whether or not there is medical benefit, the risks associated with development of a metastable form must be mitigated by laboratory work which provides assurance that (a) the largest possible form change will have no substantive effect on product quality or bioavailability, and/or (b) a change will not occur under all reasonable real-world storage conditions, and/or (c) analytical methodology and sampling procedures are in place which assure that a problem will be detected before dosage forms which have compromised quality or bioavailability can reach patients.

Keywords: Amorphism; Dissolution; Polymorphism; Dosage form; Biovailability; Stability; Mechanical properties

Contents

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doi:10.1016/j.addr.2003.10.008

1. Introduction

The subject of drug polymorphism has received extensive academic and industrial attention since the early pioneering reports of Aguiar and colleagues at Parke-Davis, in which effects of polymorphism on dissolution and bioavailability were highlighted for chloramphenicol palmitate [1,2]. Drug polymorphism has been the subject of hundreds of publications and numerous excellent reviews. For both an overview and an in-depth analysis of this complex field, see the excellent series of reviews in Volume 48 (2001) of *Advanced Drug Delivery Reviews* [4–9], in "Polymorphism in Pharmaceutical Sciences" edited by Brittain [10–19], and in "Solid State Chemistry of Drugs" by Byrn et al. [20]. In addition, two very clear reviews/commentaries from the regulatory perspective have appeared [21,22].

At this point in time, it would be difficult to say anything novel about the effects of polymorphism on physical stability, chemical stability, manufacturability, or oral absorption that has not been reviewed in the references quoted above. In many respects, the 1969 review by Haleblian and McCrone was prescient in its broad coverage of the issues of polymorphism in pharmaceuticals [23]. In this article, we make no effort to review once again the vast literature on drug polymorphism. Furthermore, we do not here discuss theoretical or experimental details of the study of polymorphism. Rather, we attempt to provide a practical perspective on the impact of polymorphism on chemical stability, manufacturability, and bioavailability, with particular attention to a limited number of illustrative cases from our experience and the literature. Such a practical perspective must involve generalizations for which there are occasional exceptions.

2. Why develop multiple polymorphs?

It is generally accepted that, during the course of development of a drug, the lowest energy crystalline polymorph should be identified and chosen for development. This is critically important because the post-approval appearance of a polymorph with lower energy than the marketed polymorph can be catastrophic, as happened with the HIV protease inhibitor ritonavir [24]. For this reason, innovator pharmaceutical companies expend significant resources on this technical issue early in the development of a new drug. When executed carefully, the search for the lowest energy polymorph is arduous and time-consuming because (a) a variety of physical and chemical measurements must be made, and the stability of physical and chemical characteristics must be established in real-time storage models, (b) this search is not trivial, because a metastable polymorph may masquerade as the most stable form, and (c) every compound is different (i.e. the identity and properties of polymorphs are not theoretically predictable at present). The search for drug polymorphs is a complex empirical exercise, although recent advances in automation promise to make this activity somewhat less labor intensive.

There are three exceptions to the dictum that only the most stable polymorph should be developed. The first is extremely rare: the situation in which the lowest energy polymorph is chemically unstable due to the juxtaposition of two reactive groups in adjacent molecules in the crystal lattice. Such a "topochemical" reaction can in principle be avoided by identification of a crystalline polymorph in which the reactive species are no longer spatially close and/or oriented in a manner conducive to reaction. We are unaware of any examples of this phenomenon in

marketed drugs. The second exception is becoming more common, that is, the case of a drug whose absorption is solubility-limited and thus cannot achieve the systemic exposure required for therapy. In this case, a more soluble form of the drug is desired to deliver the therapeutic dose. The third exception is the situation in which it is desired to increase the dissolution rate of a drug to shorten T_{max} and/or increase C_{max} in order to bring quick relief for acute symptoms.

In the authors' opinion, when confronted with low solubility or the desire to decrease T_{max} or increase C_{max}, it is generally more productive to develop a stabilized amorphous form than a metastable crystalline polymorph. This will be discussed in more detail below.

In each of these three exceptions, a metastable polymorph or amorphous form is developed to provide a medical benefit.

If there is a desire to develop a metastable polymorph or amorphous form for a reason which does not provide a medical benefit, e.g. for manufacturing ease or for some other business reason, then the developer must assure that there is no significant risk to the patient. A rigorous laboratory-based analysis of the risks involved must be undertaken. This is of course also true when there is a medical benefit. In the sections below, we discuss the issues involved in the development of metastable polymorphs and amorphous forms, and their potential practical significance.

3. Chemical stability of polymorphs and amorphous forms

The polymorphs (or pseudopolymorphs) of some drugs have been shown to exhibit different chemical stability. Examples are carbamezepine [25], paroxetine maleate [26], indomethacin [27], methyprednisolone [28], furosemide [29], and enalapril maleate [30]. For example, the photodecay of form II of carbamezepine was 5- and 1.5-fold faster than forms I and III, respectively [25]. In addition to a change in the rate of decay, polymorphism may also affect the mechanism of decay, as observed in the reactivity of different polymorphs of cinnamic acid derivatives [31].

It is generally observed that the more thermodynamically stable polymorph is more chemically stable than a metastable polymorph. This has generally been attributed to higher crystal packing density of the thermodynamically favored polymorph (i.e., the "density rule"), but recent investigation suggests that other factors, such as optimized orientation of molecules, and H-bonds and non-hydrogen bonds in the crystal lattice play a more important role. Relatively small changes in crystal packing may lead to significant differences in the crystal packing density and chemical reactivity of two polymorphs, as indomethacin polymorphs [27]. Indomethacin can exist as the metastable α-form and thermodynamically favored γ-form. As an exception to the density rule, the density of metastable α-form (1.42 g/mL) is higher than that of the γ-form (1.37 g/mL), suggesting tighter packing of the less stable polymorph. Although the metastable α-form has higher density, the α-form rapidly reacts with ammonia vapor while the γ-form is inert to ammonia. The lack in correlation between higher packing density and lower reactivity of the indomethacin polymorphs is due to the differences in crystal packing/hydrogen bonding. Higher density of the α-form is due to the presence of one extra H-bond in the crystal lattice. The differences in H-bonding and the crystal packing (two centrosymmetric carboxylic groups in α-form vs. three asymmetric molecules in γ-form) leads to a layer motif in the α-form that exposes the reactive carboxylic acid group to the crystal face, while in the γ-form, H-bonded carboxylic acid groups are buried in a hydrophobic cage. Easy accessibility of the reactive carboxylic acid groups in the α-form combined with the weak H-bond of one carboxylic acid group leads to higher reactivity of the α-form [27].

The intrinsic difference in chemical stability between two polymorphs, e.g. α- and γ-indomethacin, cannot be overcome, but a less chemically stable polymorph can often be formulated in a way which results in acceptable shelf-life.

In comparison to crystalline polymorphs, the amorphous form of a drug is generally expected to be less chemically stable due to the lack of a three dimensional crystalline lattice, higher free volume and greater molecular mobility. The chemical stability of amorphous systems has been discussed in detail elsewhere [20,32–35]. As early as 1965, amorphous penicillin G was shown to be less stable than the crystalline sodium and potassium salts [36]. Physical

change of amorphous molecules from a glassy state (at $T < T_g$) to a more mobile supercooled liquid state (at $T > T_g$) may further decrease chemical stability. For example, Asn-hexapeptide was found to be 10–100-fold more stable in the glassy state compared to its supercooled liquid state [37,38]. In addition to higher reactivity, the mechanism of degradation may be different in crystalline versus disordered materials. For example, methyl transfer was the major reaction pathway in unmilled crystalline tetraglycine methyl ester (TGME), while polycondensation was the major reaction pathway in milled TGME [39]. This change in mechanism from methyl transfer to polycondensation upon milling may be due to the creation of a disordered state with higher free volume where molecules can undergo the much higher change in orientation that is needed for the polycondensation reaction [39].

It should be pointed out that a major portion of any formulation effort is the choice of excipients and processes which minimize the chemical instability of the drug. If a metastable polymorph (or amorphous form) is less chemically stable than the lowest energy form of the drug, then in many cases it will be possible to maximize the chemical stability of this metastable form through judicious formulation decisions [40–45]. Thus reduced chemical stability of a metastable crystalline or amorphous drug form does not necessarily preclude its development as a product.

For a more in-depth review of chemical stability and drug physical state, see Byrn et al. [9,20].

4. Mechanical properties of polymorphs and amorphous drug forms

Polymorphism can affect the mechanical properties of drug particles, and thus may impact the manufacturability and physical attributes of tablets. For example, polymorphs of metoprolol tartrate [46], paracetamol [47–50], sulfamerazine [51], phenobarbitone [52], carbamazepine [53,54], phenylbutazone [55] and other drugs have been shown to exhibit different mechanical properties. A common effect of polymorphism is alteration of powder flow due to the difference in particle morphology of two polymorphs. Polymorphs with needle- or rod-shaped particles may have poor flow compared to polymorphs with low aspect ratio, e.g. cubic habit or irregular spheres. The effect of polymorphism on other mechanical properties, such as hardness, yield pressure, elasticity, compressibility and bonding strength is more complex.

A simple general rule, although semi-empirical, proposed more than 20 years ago by Summers et al. can be used to predict the effect of crystal packing of polymorphs on their compressibility and bonding strength [55,56]. The more stable polymorph, due to its higher packing density, is expected to form stronger interparticle bonds but is harder to deform [46,55,56]. Since an increase in the bonding surface area resulting from deformation of particles may have higher impact on tablet strength than interparticle bond strength, the more stable of two polymorphs may provide weaker tablets. The mechanical properties of two enantiotropic polymorphs of metoprolol tartrate, metastable form I and the more stable form II (at room temperature), are consistent with this rule [46]. The porosity of pure drug tablets and yield pressure for form I were lower than for form II, suggesting that the less dense metastable form I may have less strength in the crystal lattice and be easier to deform. Form I also had higher elastic recovery, probably due to higher elasticity of form I and/or lower porosity of the tablets. As predicted, the tablets of the metastable form I were stronger at low pressures than those of form II, probably due to the higher compressibility of form I.

Factors other than those accounted for by the general rule proposed by Summers et al. may also affect the mechanical properties of two polymorphs. For example, the presence of slip planes in form I of sulfamerazine was found to be the reason for its higher plasticity than form II, the more stable form at room temperature [51]. This higher plasticity results in greater compressibility and tabletability. The authors of this study generalized this observation and suggested that crystals with slip planes would be expected to have superior tableting performance [51]. Recently, a fundamental atom–atom potential model simulation was used to predict a few mechanical properties of sulfathiazole and carbamezepine polymorphs [53]. More fundamental research in this area will improve our ability to predict the effect of polymorphism on mechanical properties.

For amorphous drug forms, mechanical properties may be different from those of crystalline drug due to

the absence of long range packing. The mechanical attributes of amorphous forms are less well understood than those of crystalline polymorphs. The lack of information on mechanical properties of amorphous drugs may be due to the physical and chemical instability of these forms, leading to reluctance in developing an amorphous form for a commercial drug product. Thus, an evaluation of mechanical properties of amorphous drugs is not routinely investigated in the pharmaceutical industry. One report comparing the mechanical properties of crystalline and amorphous forms of a model drug was published last year [57]. Compacts of amorphous material had higher brittleness and elasticity, and lower ductility than compacts prepared with the crystalline form.

Differences in the mechanical properties of two polymorphs or amorphous versus crystalline forms may or may not affect the manufacturability and physical attributes of tablets. For example, in the case of metoprolol tartrate, the differences in the mechanical properties of two polymorphs did not affect the bonding properties of tablets with relatively high drug loading [46]. The extent of the difference in the mechanical properties of two polymorphs, the drug loading, the robustness of each manufacturing step and the absolute value of the mechanical property undergoing change may be important parameters to consider while assessing the impact of polymorphism on manufacturability and physical attributes of tablets.

In some cases the favorable mechanical properties of one polymorph, even a metastable one, may be used to develop a more desirable process to manufacture tablets. For example, direct compression may be used to manufacture tablets with the more compressible orthorhombic form II of paracetamol instead of using more resource intensive granulation processes for monoclinic form I [47,50]. However, development of a metastable form for processing advantage should only be undertaken for drugs for which a very complete understanding exists with respect to form-dependent chemical stability, physical stability, and most importantly, bioavailability. This will typically be the case only for very old, highly studied, drugs.

As discussed above for chemical stability, manufacturability deficits of a particular polymorph may be overcome through judicious selection of excipients and processes. If a stable polymorph has problematic mechanical properties, this certainly does not preclude its development. It is much more preferable to use excipients and processing to overcome the mechanical deficits of a stable polymorph than to develop an unstable polymorph because of its better mechanical properties.

For a review of the effects of processing (e.g. tableting) on drug form, see Morris et al. [8] and Brittain and Fiese [17]. For a discussion of the use of excipients to compensate for the physical properties of drugs in formulations, see Amidon [58].

5. Bioavailability of polymorphs

There are many reports of polymorph-dependent bioavailability and/or absorption rate, with much of this work done in animals. See for example animal studies of chloramphenicol palmitate [59], phenylbutazone [60], amobarbitol [61], cimetidine [62], 6-mercaptopurine [63], and chlortetracycline [64]. For the purpose of the present analysis, we consider only human studies in detail.

5.1. Effects of polymorphism on dissolution and oral drug absorption in humans

Among the best known cases involving human dosing are those of chloramphenicol palmitate, mefenamic acid, oxytetracycline, and carbamazepine. These observations are quite old, having been reported in the 1950s and 1960s. For example, Aguiar et al. [1] demonstrated that absorption of chloramphenicol palmitate polymorph B was significantly greater than absorption of polymorph A in humans. Peak chloramphenicol serum levels were linearly proportional to the percentage of Form B in Form A/Form B mixtures. Chloramphenicol palmitate is a prodrug of chloramphenicol, which was prepared to provide a tasteless derivative [65]. Glazko et al. [66] reported that chloramphenicol palmitate must be hydrolyzed by intestinal esterases before the drug could be absorbed. Aguiar and colleagues demonstrated that in vitro hydrolysis of this prodrug by pancreatin was polymorph dependent, with significant hydrolysis of polymorph B and little hydrolysis of polymorph A. Aguiar and Zelmer [2] demonstrated that Form B dissolves faster than Form A, and has a much higher

solubility. This solubility difference probably results in the difference in ester hydrolysis rates, and ultimately the difference in oral absorption.

Aguiar and Zelmer [2] also reported on human absorption of two polymorphs of mefenamic acid. In this case, the two polymorphs gave almost identical blood levels. Aguiar and Zelmer calculated a free energy difference (ΔG_T) of −251 cal/mol between the two mefenamic acid polymorphs, where

$$\Delta G_T = RT \ln (\text{Solubility A}/\text{Solubility B})$$

In a similar manner, they calculated a free energy difference of −774 cal/mol between polymorphs A and B of chloramphenicol palmitate. These authors pointed out the correlation between the free energy difference and the observation of a polymorph-derived bioavailability difference (seen for chloramphenicol palmitate but not for mefenamic acid). However, the situation is clearly complicated by the issue of hydrolysis of the palmitate moiety in the lumen for chloramphenicol palmitate.

Brice and Hammer [67] reported in 1969 that oral dosing of 16 lots of oxytetracycline capsules from 13 suppliers gave drug blood levels which were lower than the innovator product. Seven of the lots gave oxytetracycline blood levels which were lower than the generally accepted minimum therapeutic level. Blood levels were generally correlated with in vitro dissolution rate. Groves subsequently reported large differences in in vitro dissolution performance of oxytetracycline tablets from various sources [68]. These studies made no attempt to relate dissolution observations to oxytetracycline polymorphism, and the observed differences may have resulted from differing formulations rather than differing polymorphs. Recently, Liebenberg et al. [69] compared six bulk oxytetracycline samples which met USP specifications, and noted that four of these contained one polymorph while the other two contained a different polymorph (form A). Tablets prepared from the form A polymorph dissolved significantly more slowly than the others in 0.1 M HCl. For example, the form A tablets exhibited ~55% dissolution at 30 min, while the others exhibited complete (~95%) dissolution at 30 min.

The drug carbamazepine exhibits polymorphism and product-to-product dissolution and bioavailability differences, but a connection between these phenomena has not been directly experimentally demonstrated. Kahela et al. [70] reported that the anhydrous and dihydrate forms of carbamazepine exhibited very similar pharmacokinetics in humans. While the anhydrous form exhibited slower in vitro dissolution than the dihydrate in 0.1 M HCl, inclusion of 0.01% polysorbate 80 in the dissolution medium essentially eliminated this difference. Another study by Jumao-as et al. [71] demonstrated no difference in bioavailability between a generic carbamazepine product and the innovator product. Regardless, carbamazepine therapy with some products has been reported to be problematic [72,73]. Meyer et al. [74] reported on in vitro/in vivo studies of three out of 53 batches of generic carbamazepine tablets which were recalled due to clinical failures and dissolution changes. In vitro dissolution testing, carried out in water containing 1% sodium lauryl sulfate, revealed that two of the batches dissolved more slowly than the innovator product, and one batch dissolved more quickly. While the innovator product gave ~95% dissolution in 90 min in this medium, the slower generic batches gave ~35% and 75% dissolution. In humans, the generic batches gave mean relative AUCs (relative to the innovator) of 60–113%, with the same rank order observed in the in vitro dissolution behavior. It was suggested that moisture uptake during storage and particle size differences may have been involved in the irreproducible behavior of the generic tablets of this practically insoluble drug. It is known that anhydrous carbamazepine converts to the dihydrate quickly, e.g. completely within 1 h, when the anhydrous form is suspended in water [75].

The mechanistic uncertainty in these examples (i.e. whether drug physical form was involved in the observed dissolution or bioavailability differences) results from the lack of spectroscopic data which can identify the drug polymorph in a complex dosage form. Modern techniques such as ss-NMR and NIR can identify polymorphs in dosage forms (within limits), and should facilitate increased mechanistic understanding in future studies.

It is clear that for some drugs, there will be polymorph-dependent bioavailability. For a larger group, there will be polymorph-dependent absorption rate, reflected in in vivo C_{max}. For some pairs of polymorphs, there will be pharmacokinetic bioequi-

valence. As described above, in 1969 Aguiar and Zelmer proposed that polymorphs with a large free energy difference between them are likely to differ in pharmacokinetic behavior. This simply reflects a difference in solubility. In addition, polymorphs may exhibit different dissolution rates because of their different crystal habits, and this may also contribute to in vivo absorption rate differences.

For an excellent in-depth review of the relationships between polymorphism and solubility and dissolution rate, see Brittain and Grant [16].

5.2. The role of dose in bioavailability of high energy polymorphs

A significant solubility difference between two polymorphs is likely to result in a difference in oral absorption rate, reflected in a difference in C_{max}. Differences in AUC, or oral bioavailability, will occur less often, and will depend upon the same underlying principles which govern the bioavailability differences between two unrelated drugs. Drug absorption may be modeled in a variety of ways [76,77]. A simple context in which to discuss this issue is provided by the concept of the maximum absorbable dose (MAD) [3,78]. The MAD is a conceptual tool which represents the quantity of drug which could be absorbed if the small intestine could be saturated with drug for 4.5 h (270 min), the average small intestinal transit time.

$$\mathrm{MAD} = S \times K_a \times \mathrm{SIWV} \times \mathrm{SITT}$$

S, solubility (mg/ml) at pH 6.5; K_a, transintestinal absorption rate constant (min^{-1}); SIWV, small intestinal water volume (ml); SITT, small intestinal transit time (min).

The solubility at pH 6.5 reflects the solubility in the small intestine. K_a is determined in a rat intestinal perfusion experiment. In our laboratories, it has been observed that the human K_a is 1.4 times the rat K_a [79]. SIWV is the amount of water available for dissolution, generally accepted to be ~250 ml. While SIWV and SITT are approximations, moderate variations in these parameters do not significantly affect this analysis. The resulting MAD is in mg. This analysis ignores first pass intestinal and hepatic metabolism, which can be saturated, thus affecting bioavailability.

Table 1
MAD

Rat K_a (min^{-1}) [Human K_a]	Solubility (mg/ml)	MAD (mg) (Human)
0.003 [0.004]	0.01	2.7
0.003 [0.004]	0.02	5.4
0.003 [0.004]	0.03	8.1
0.03 [0.04]	0.01	27
0.03 [0.04]	0.02	54
0.03 [0.04]	0.03	81

If the intent is to increase bioavailability, it can be readily seen that increasing drug solubility will result in increased MAD (Table 1). In general, the range of solubility differences between polymorphs is typically 2–3-fold, due to the relatively small difference in free energy between polymorphs. Thus a higher energy polymorph with a solubility which is 3× that of the lowest energy polymorph may give a systemic exposure which is 3× that given by the low energy polymorph. As shown in Table 1, for a low human K_a of 0.004 min^{-1}, and a solubility of 0.01 mg/ml, a 3-fold increase in solubility only results in a MAD of 8.1 mg, which would be inadequate if the desired absorbed dose were, say, 50 mg. If bioavailability were practically governed in this way, there would not be much opportunity to increase the bioavailability of low-solubility drugs by developing a high energy polymorph or amorphous form.

In fact, equilibrium solubility may not be very relevant for oral absorption enhancement if polymorphs (or pseudopolymorphs) are physically unstable in the aqueous environment. Instead, intrinsic dissolution rate (IDR) and kinetic solubility over 4–6 h may be more relevant parameters to consider while studying the oral absorption of polymorphs. Form changes may sometimes occur during IDR and kinetic solubility measurements, but these changes are occurring on a timescale relevant for oral absorption, i.e. the small intestinal transit time. The kinetic solubility of a metastable polymorph over 4–6 h is often higher than its equilibrium solubility. The rank order of the IDR of polymorphs has been found to correlate well with the rank order for oral absorption due to the faster rate of dissolution of the less stable polymorph, leading to higher concentration of drug in solution available for absorption. Generally, this may

lead to a higher in vivo C_{max}, but not a higher AUC, unless the drug is present in suspension throughout its small intestinal transit time (i.e. the dose is substantially greater than the MAD calculated for the thermodynamically stable polymorph). In some circumstances, the IDR and the achievable metastable supersaturation may temporarily provide a maximum drug concentration in the intestinal lumen which is in excess of the equilibrium solubility of the high energy polymorph. If the drug does not rapidly precipitate in the GI lumen, then the achievable MAD can conceivably be very large.

Although IDR may be a good single parameter to describe relative dissolution rates of two polymorphs, this does not take into account other factors that may govern oral absorption, namely, rate of conversion of one polymorph to another less soluble polymorph in the GI lumen, and the resulting precipitation of drug in the GI fluid. It is generally not possible to theoretically predict the degree of supersaturation of drug from a metastable polymorph or amorphous form, or the kinetics of physical conversion of one polymorph to another. However, these processes may be quantified by comparing the extent of supersaturation in model GI fluid according to Eq. (1), and more importantly Eq. (2):

Supersaturated concentration ratio (SCR)

$$= C_{max,\ form\ 1}/C_{max,\ form\ 2} \quad (1)$$

Supersaturated AUC ratio (SAR)

$$= AUC_{form\ 1}/AUC_{form\ 2} \quad (2)$$

where $C_{max,\ form\ 1}$ and $C_{max,\ form\ 2}$ are the in vitro maximum concentrations of drug in solution from forms 1 and 2, respectively; and $AUC_{form\ 1}$ and $AUC_{form\ 2}$ are the areas under the in vitro drug concentration versus time curve over, say, 6 h, for forms 1 and 2, respectively. If a high dose (in substantial excess of the MAD for the stable polymorph) is dosed, and supersaturation is maintained for a long time, e.g. 6 h, while drug is absorbed, then the potential exists to achieve absorption of an amount of drug much higher than the MAD for the stable polymorph.

The greatest effect of dissolution rate and supersaturation of drug from a polymorph or amorphous form is expected for compounds with high permeability and low solubility relative to dose (i.e. BCS class II compounds, where the administered dose will remain as a suspension for most of the absorption period). For solutes where the dose is expected to be very soluble in the GI fluid (i.e. BCS class I and III compounds) there may be no, or minimal differences in the AUC of polymorphs because solubility is not expected to be rate limiting in oral absorption.

5.3. Potential effects of physical instability of a metastable polymorph on oral absorption

Developing a bioequivalent product with a metastable form may not be easy, but in some cases it may be possible using formulation methods to achieve a bioequivalent AUC. It may be trickier, but possible, to blunt the higher pharmacokinetic C_{max} which results from the higher dissolution rate of the metastable form. Thus, it may be possible to develop a formulation with a metastable drug form which is bioequivalent to the innovator formulation containing the thermodynamically most stable form. For some drugs, there is a potential danger that bioavailability could be lost if the metastable form converts to the more stable form during the shelf-life of the product. This is illustrated in Table 2. A metastable drug form may be formulated in a product (e.g. tablet) which has the same dissolution rate (Y) as a formulation of the stable drug form. Of course the metastable drug product will have to be formulated in a way which slows the drug dissolution rate. If the metastable form converts to the stable form in the product on storage, then the dissolution rate may decrease and in vivo performance may be compromised. This compromised in vivo performance may involve increased pharmacokinetic

Table 2
Potential performance changes on storage of a dosage form containing a metastable drug form

Drug form in formulation	IDR	Dissolution rate in formulated product	Dissolution rate in product after storage if metastable form converts to stable form
Metastable	$X+\Delta X$	Y	$Y-\Delta Y$
Stable	X	Y	Y

variability and, more extremely, decreased C_{max} and bioavailability.

As an example, phenylbutazone Form C exhibits a dissolution rate and solubility which are 1.5 × and 1.2 × that of Form A, respectively [80]. On storage at 40 °C for 12 months, Form C was converted to 60% Form A. As another example, various marketed tablet formulations of glibenclamide have been shown to exhibit differing in vitro dissolution [81]. Glibenclamide exhibits forms which differ greater than 10-fold in solubility in simulated gastric fluid [82]. However, for glibenclamide the connection between product-to-product variability and polymorphism has not been directly demonstrated, but provides a possible explanation.

6. Dosage form decision

6.1. Metastable crystalline polymorph versus amorphous form

As discussed above, metastable crystalline polymorphs and amorphous forms may be less chemically stable and potentially possess different (in some cases less desirable) mechanical properties than the related stable crystalline form. These potential problems can in theory be solved by judicious choice of excipients and appropriate formulation strategies. In addition to chemical instability and mechanical properties, physical stability of the drug during product shelf life is of paramount importance in developing a drug product. A change in physical form can not only affect chemical stability and mechanical attributes of tablets, but much more importantly can compromise the oral absorption of a drug via a change in solubility.

Physical stabilization of intrinsically physically unstable crystalline polymorphs is a challenge because, by definition, the use of additives for improvement of physical stability involves a two phase system (polymorph and stabilizer) where the drug molecules are not in intimate contact with the stabilizer. Furthermore, physical conversion can be relatively precipitous, and exceptional care must be taken to design stability studies which cover all reasonable real-world conditions which such a formulation may encounter (e.g. temperature cycling). There is a need for increased understanding of stabilization of metastable crystalline forms, and research in this area is sorely needed if practical solutions are to be found.

Amorphous forms are of course also physically unstable. For an introduction to the literature and general concepts on the physical stability of amorphous forms see Yu [5], Yoshioka et al. [83], and Crowley and Zografi [84]. Physical stabilization of amorphous forms is possible in some situations by generating intimate contact between the amorphous drug and the stabilizer by creating a drug/stabilizer dispersion [85–88]. The use of such dispersions, particularly with polymers, to intentionally enhance drug solubility has been known for many years [89,90], and practical formulations which achieve facile low-solubility drug dissolution and supersaturation have recently been described [91,92]. The identification of pharmaceutically acceptable stabilizers and processes which can inhibit solid state crystallization for a reasonable shelf-life is also a recent development [86].

While stabilized amorphous forms can sometimes be developed for intentional bioavailability improvement, the use of such forms to provide a dosage form which is bioequivalent to the stable drug crystalline form would be difficult, but perhaps possible in certain situations.

7. Solvates and hydrates

In general, the analysis provided above for the behavior of polymorphs also applies to metastable solvates and hydrates. For example, the dissolution rate and solubility of a drug can differ significantly for different solvates. Glibenclamide has been isolated as pentanol and toluene solvates, and these solvates exhibit higher solubility and dissolution rate than two non-solvated polymorphs [93]. In formulation of solvates (other than hydrates), the formulator must be careful to address the toxicity of the associated solvent, and carefully evaluate interactions of the drug and mobile solvent molecules with excipients on storage, which may result in compromised performance.

Similar to polymorphs in general, the physical stability of hydrates and anhydrous forms may depend upon the relative humidity and/or temperature of the environment, and the most stable form may switch as

the humidity/temperature is varied. Anhydrous to hydrate transitions can occur during dissolution at the drug/medium interface and can affect dissolution rate and perhaps bioavailability. Discussion of these issues is beyond the intended scope of this review.

Pharmaceutical solvates and hydrates have been reviewed by Morris [13], and hydrates have been reviewed by Khankari and Grant [94].

8. Conclusions

In principle, any polymorph or hydrate/solvate or amorphous form of a drug can be appropriately formulated. In practice, for some drugs constraints may be encountered. In general, the following conclusions are drawn from the literature and the experience of the authors:

1. It is always advisable to identify the lowest energy crystalline polymorph of a drug candidate during development, and to develop this form. While this form may not be the most processable form available, processing deficits can almost always be overcome with judicious choice of excipients and formulation processes. The lowest energy polymorph is almost always the most chemically stable form, and will not convert to another polymorph during storage as drug product. Of course, care must be taken to avoid conversion during processing to a physically metastable, perhaps chemically unstable, form.
2. Metastable crystalline polymorphs may be less chemically stable than the most physically stable crystalline form. Likewise, amorphous drug forms will generally be less chemically stable than the most physically stable form. It is often possible to improve chemical stability of such forms through judicious choice of excipients and formulation processes.
3. If a developer is precluded from developing the lowest energy drug form, for medical benefit or otherwise, it is preferable to develop a stabilized amorphous form, e.g. as a dispersion. Development of a metastable crystalline or amorphous form as a standard physical mixture or granulation with excipients is less preferable, because it is difficult to guarantee that such a formulation will resist form changes on storage. If the metastable form converts to the stable less soluble form in the dosage form on storage, then in vivo C_{max} will almost certainly decrease, and in vivo AUC may also decrease depending upon where the drug lies in dose–solubility–permeability space. However, there will be occasional exceptions in which an unstabilized amorphous or metastable crystalline polymorph will be physically stable over the shelf-life of a formulation.

In the end, the manufacturer, whether innovator or generic, must guarantee the quality and bioavailability of the dosage form. It is highly desirable that the drug physical form not change over the storage life of the drug product. If the physical form does change, or if it could change, then the manufacturer must provide assurance (a) that the largest possible change would have no substantive effect on product quality or bioavailability, and/or (b) that extensive scientific study of the formulation guarantees that a change will not occur under all reasonable real-world storage conditions, and/or (c) that analytical methodology and sampling procedures are in place which guarantee that a problem will be detected before dosage forms which have compromised quality or bioavailability can reach patients.

Acknowledgements

We thank Ravi Shanker and Bruno Hancock of Pfizer for very helpful reviews of our manuscript. We also thank Andre Raw of FDA and the anonymous reviewers for comments which helped us communicate our practical perspective with more clarity.

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